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Corticosteroids or immunosuppressants were not superior to supportive care in IgA nephropathy patients with mild proteinuria

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Abstract

Background: We aimed to evaluate the effect of immunosuppressant therapy for immunoglobulin A nephropathy (IgAN) patients with mild proteinuria (<1 g/d).

Methods: We recruited patients with biopsy-proven IgAN from 4 study centers. Patients were followed for more than 1 year or up to the study end point. Clinical indexes, renal pathological data, and treatment information were collected during the follow-up period. IgAN patients with mild proteinuria (<1 g/d at biopsy) were included. Patients were divided into a supportive care group (SC) and an immunosuppressant group (IT). Patients in the SC group received the optimal dose of renin angiotensin system inhibitors (RASi). Patients in the IT group received corticosteroids or immunosuppressant therapy plus RASi. Responses to therapy included complete remission (CR), partial remission (PR), no response (NR), and end stage renal disease (ESRD). A 50% decline in estimated glomerular filtration rate (eGFR) and/or ESRD was the primary end point of this study.

Results: 295 patients (36.3% male and 63.7% female) were included in this study and were followed for 49.46 ± 24.35 months. We found a significant difference in estimated glomerular filtration rate, urine protein, mesangial hypercellularity, segmental glomerulosclerosis, cellular or fibrocellular crescents, and glomerulosclerosis between the 2 treatment groups at baseline. At the final follow-up, 224 patients (75.9%) achieved CR, 7 patients (2.4%) achieved PR, 55 patients (18.6%) had NR, and 9 patients (3.1%) reached ESRD. However, no significant differences were observed between the SC and IT groups with respect to CR (76.4% vs 73.5%, $P = .659$), PR (2.0% vs 4.1%, $P = .329$), NR (18.3% vs 20.4%, $P = .728$), and ESRD (3.3% vs 2.0%, $P = 1.000$). Kidney survival rates were also comparable between the SC and IT groups (93.7% vs 94.1%, $P = .808$). We observed similar results after subgroup analysis according to chronic kidney disease stages or pathological manifestations. A multivariate model showed that segmental sclerosis (HR 9.55, 95% CI 1.04–88.16, $P = .047$) and glomerulosclerosis (HR 21.09, 95% CI 1.39–320.53, $P = .028$) were independent predictors of poor renal survival.

Conclusions: Corticosteroids or immunosuppressants were not superior to supportive care in IgA nephropathy patients with mild proteinuria.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor, Alb = serum albumin, ARB = angiotensin receptor blockers, C = crescents, CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CR = complete remission, DBP = diastolic blood pressure, E = endocapillary proliferation, eGFR = estimated glomerular filtration rate, ESRD = end stage renal disease, IgAN = Immunoglobulin A nephropathy, IT = immunosuppressive therapy, KDIGO = Kidney Disease Improving Global Outcome, M = mesangial proliferation, NR = no response, PR = partial remission, RASBs = renin angiotensin system blockades, RASi = renin angiotensin system inhibitors, S = segmental sclerosis, SBP = systolic blood pressur, SC = supportive care

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GP and JT contributed equally to this work.

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This study was registered at Clinical Trail Registration Center of China (www.ClinicalTrials.gov; TCTR20180313004).

This study was approved by the Ethics Committee of West China Hospital of Sichuan University and was in accordance with the Helsinki Declaration.

Written informed consent was obtained from all individual participants in this study.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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group, Scr = serum creatinine, SLE = systemic lupus erythematosus, T = tubular atrophy/interstitial fibrosis, TA-P = time-averaged proteinuria.

Keywords: corticosteroids, IgA nephropathy, immunosuppressive therapy, proteinuria, renal survival, supportive care

1. Introduction

IgA nephropathy (IgAN) is one of the most common primary chronic glomerular diseases worldwide, especially in Asia.[1] The major pathologic feature is predominant IgA deposits in the glomerular mesangium, which are highly variable in clinical presentation and outcome.[2] In 20% to 40% of patients with IgAN, slow progression to end stage renal disease (ESRD) occurs over 20 years from diagnosis.[3] The majority of clinical trials and guidelines have focused on patients with active disease characterized as proteinuria greater than 1 g daily.[4] No study has analyzed treatment of IgAN patients with proteinuria < 1 g/d. Given that corticosteroids or immunosuppressants are widely used in patients that present with heterogeneous clinical and pathological disease manifestation,[5,6] we performed this study to analyze the safety and efficacy of steroids or immunosuppressants in IgAN patients with proteinuria < 1 g/d.

2. Methods

2.1. Study participants

Three hundred forty adult patients (33.15 ± 9.22 years) with newly diagnosed biopsy-proven IgAN were retrospectively enrolled in this study between December 2007 and February 2016 from 4 Chinese study centers (West China Hospital of Sichuan University, Affiliated Hospital of Zunyi Medical College, the Third Hospital of Zigong City, and People's Hospital of Mianzu City). Patients with proteinuria < 1 g/d at biopsy were included. The exclusion criteria were as follows:

(1) systemic diseases such as ankylosing spondylitis, systemic lupus erythematosus (SLE), diabetes mellitus, Henoch–Schönlein purpura, liver cirrhosis, and others;
(2) follow-up period < 12 months before reaching the study's defined endpoint;
(3) missing data during follow-up;
(4) history of kidney transplantation or use of corticosteroids, immunosuppressants, or fish oil prior to renal biopsy.

Treatment regimen was selected based on patients' willingness and doctors' experience. Every patient signed written informed consent. This study adhered to the Helsinki Declaration and was approved by the Ethics Committee of West China Hospital of Sichuan University. This study was registered at the Clinical Trail Registration Center of China (www.ClinicalTrials.gov; TCTR20180313004).

2.2. Follow-up and data collection

The follow-up period refers to the interval between renal biopsy and the last outpatient visit, death, ESRD, or reaching the defined end point. At the time of biopsy and during follow-up, sex, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine (Scr), estimated glomerular filtration rate (eGFR), serum albumin (Alb), 24-hour proteinuria, kidney pathology data, and the use of antihypertensive drugs, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), corticosteroids, or immunosuppressants were recorded. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Renal biopsy was reviewed by an experienced pathologist and nephrologist using the Oxford Classification of IgAN:[7] mesangial score < 0.5 or >0.5 (M0/M1), segmental glomerulosclerosis absent or present (S0/S1), endocapillary hypercellularity absent or present (E0/E1), tubular atrophy/ interstitial fibrosis < 25%, 26% to 50%, >50% (T0/T1/T2), and cellular or fibrocellular crescents absent, or a crescent in at least 1 glomerulus, or crescents in at least 25% of glomeruli (C0/C1/C2). Specially, global glomerulosclerosis (G) was defined as a hyaline deposition or scarring lesion occurring in more than 50% of any 1 glomerulus and was graded according to the percentage of global glomerulosclerosis: G0 (≤25% of glomeruli), G1 (26–50% of glomeruli), and G2 (>50% of glomeruli).

2.3. Clinical responses and outcomes

Patients were divided into 2 groups according to therapeutic strategy. Patients in the supportive care group (SC) received only the optimal dose of ACEI or ARB to achieve target blood pressure (BP < 130/80 mm Hg). Patients in the corticosteroids or immunosuppressant group (IT) received optimal ACEI/ARB plus corticosteroids (0.5–1 mg/kg/d prednisone or equal dose of methylprednisolone, tapering down within 6–8 months) with or without immunosuppressant therapy (2 mg/kg/d cyclophosphamide for 3 months or 1–2 g/d mycophenolate mofetil for 6–8 months).

Responses to therapy included complete remission (CR), partial remission (PR), no response (NR), and ESRD. CR was defined as urinary protein excretion < 0.5 g/24 h with an eGFR decrease less than 10% of baseline. PR was defined as decreased proteinuria >50% of baseline with eGFR decreased to less than 10% of baseline. NR was defined as decreased proteinuria < 50% of baseline or eGFR decreased to >10% of baseline. ESRD was defined as eGFR < 15 mL/min/1.73 m^2, chronic dialysis, or renal transplantation. The primary study endpoint was a renal function decline of >50% in eGFR and/or ESRD.

2.4. Statistical analyses

Categorical variables are presented as frequencies and percentages and were compared using Fisher and Chi-squared tests. Continuous variables are expressed as mean ± standard deviation (SD) and analyzed using a *t* test, 1-way ANOVA, or Kruskal–Wallis *H* test, as appropriate. Kidney survival for each group was estimated using the Kaplan–Meier method with a log-rank test. Univariate and multivariate Cox proportional hazard models were run to assess the influence of clinical and pathological variables on renal outcomes. IBM SPSS Statistics 22.0 was used for statistical analysis and a *P* value < .05 was considered significant.

Table 1

Baseline clinicopathological characteristics of IgAN patients in different theropies.

Characteristics	Groups		*P* value
	SC (n = 246)	IT (n = 49)	
Follow up (mo)	49.46 ± 24.35		
Clinical			
Male gender (%)	92 (37.4)	15 (30.6)	.367
Age (yr)	32.71 ± 10.10	35.35 ± 8.76	.089
Hypertension (%)	58 (23.6)	14 (28.6)	.457
SBP (mm Hg)	125.38 ± 19.47	129.16 ± 16.85	.205
DBP (mm Hg)	80.01 ± 13.90	80.76 ± 14.07	.733
Serum creatinine (μmol/L)	78.86 ± 27.67	86.81 ± 27.29	.067
eGFR (mL/min/1.73 m^2)	101.18 ± 27.0	88.29 ± 26.49	.002
Urine protein (g/24 h)	0.51 ± 0.24	0.65 ± 0.22	<.001
Serum albumin (g/L)	43.32 ± 21.51	41.51 ± 4.20	.559
CKD stage			0.160
Stage 1 (%)	167 (67.9)	27 (55.1)	.225
Stage 2 (%)	60 (24.4)	15 (30.6)	.642
Stage 3 (%)	19 (7.7)	7 (14.3)	.283
Pathologic (Oxford classification)			
M1 (%)	158 (64.2)	41 (83.7)	.008
E1 (%)	1 (0.4)	1 (2.0)	.305
S1 (%)	88 (35.8)	28 (57.1)	.005
T1/T2 (%)	16 (6.5)	8 (16.3)	.039
C1/C2 (%)	29 (11.8)	14 (28.6)	.002
G1/G2 (%)	27 (11.0)	17 (34.7)	<.001
Immunosuppressive therapy (%)			
Corticosteroids alone		25 (51.0)	
Corticosteroids + immunosuppresants		24 (49.0)	

Data presented as number (percentage) or mean ± SD or median.

C = crescents, CKD = chronic kidney disease, DBP = diastolic blood pressure, E = endocapillary proliferation, eGFR = estimated glomerular filtration rate, G = glomerulosclerosis, IT = immunosuppressive therapy, M = mesangial proliferation, S = segmental sclerosis, SBP = systolic blood pressure, SC = supportive care group, T = tubular atrophy/interstitial fibrosis.

3. Results

3.1. Baseline characteristics

The patients' baseline characteristics are presented in Tables 1 and 2. A total of 340 IgAN patients were screened and 295 patients with urine protein < 1 g/24 h at biopsy were included. Forty-five patients were excluded according to the following exclusion criteria: hepatitis (n = 13), diabetes mellitus (n = 6), Henoch–Schönlein purpura (n = 1), ankylosing spondylitis (n = 4), SLE (n = 1), pulmonary tuberculosis (n = 1), thalassemia (n = 1), hypothyroidism (n = 1), prior thyroid cancer operation (n = 1), multiple myeloma (n = 1), thyroid carcinoma (n = 1), tonsillectomy (n = 2), and inadequate data (n = 12) (Fig. 1). Patients were followed for 49.46 ± 24.35 months. Among the 295 patients, 194 (65.76%) had stage 1 CKD, 75 (25.42%) had stage 2 CKD, and 26 (8.82%) had stage 3 CKD. Two hundred forty-six patients (83.39%) were assigned to the SC group and 49 patients (16.61%) were assigned to the IT group according to therapeutic strategy. Twenty-five patients in the IT group received corticosteroid mono-therapy and the remaining 24 patients were treated with corticosteroids and immunosuppressant therapy. At baseline, patients in the IT group presented with significantly lower eGFR, higher 24-hour proteinuria, and more severe renal pathologic lesions (M, S, T, C, and G) than those in the SC group. Additionally, we observed significant differences in hypertension, SBP, DBP, serum creatinine, eGFR, 24-hour proteinuria, and pathologic lesion M, S, T, and G scores among patients in CKD stage 1, 2, and 3. At the end of follow-up, there were no significant differences between the SC and IT groups in serum creatinine (86.19 ± 63.49 vs 88.08 ± 30.28, $P = .839$), 24-hour urine protein (0.53 ± 0.74 vs 0.49 ± 0.44, $P = .727$), or serum albumin (43.12 ± 3.12 vs 42.94 ± 3.02, $P = .714$).

3.2. Clinical response and outcome

At the end of follow-up, 224 patients (75.9%) achieved CR, 7 patients (2.4%) achieved PR, 55 patients (18.6%) had NR, and 9

Table 2

Baseline clinicopathological characteristics of IgAN patients in different CKD stages.

Characteristics	Groups			*P* (general)
	CKD 1 n = 194	CKD 2 n = 75	CKD 3 n = 26	
Male gender (%)	70 (36.1)	28 (37.3)	9 (34.6)	.965
Age (yr)	30.37 ± 9.23	38.31 ± 9.59	39.00 ± 7.25	<.001
Hypertension (%)	40 (20.6)	20 (26.7)	12 (46.2)	.015
SBP (mm Hg)	123.42 ± 18.08	128.67 ± 19.63	137.65 ± 20.12	.001
DBP (mm Hg)	78.54 ± 12.66	80.85 ± 15.51	89.96 ± 14.23	<.001
Serum creatinine (μmol/L)	66.62 ± 13.28	93.37 ± 16.79	143.34 ± 27.24	<.001
eGFR (mL/min/1.73 m^2)	115.04 ± 15.80	76.30 ± 8.46	45.25 ± 8.39	<.001
Urine protein (g/24h)	0.51 ± 0.24	0.57 ± 0.23	0.63 ± 0.24	.010
Serum albumin (g/L)	42.17 ± 3.96	45.93 ± 38.59	40.94 ± 3.21	.321
Pathologic (Oxford classification)				
M1 (%)	123 (63.4)	55 (73.3)	21 (80.8)	.094
E1 (%)	1 (0.5)	1 (1.3)	0 (0)	.568
S1 (%)	65 (33.5)	37 (49.3)	14 (53.8)	.017
T1/T2 (%)	5 (2.6)	9 (12.0)	10 (38.5)	<.001
C1/C2 (%)	30 (15.5)	8 (10.7)	5 (19.2)	.475
G1/G2 (%)	15 (7.7)	15 (20.0)	14 (53.8)	<.001

Data presented as number (percentage) or mean ± SD or median.

C = crescents, CKD = chronic kidney disease, DBP = diastolic blood pressure, E = endocapillary proliferation, eGFR = estimated glomerular filtration rate, G = glomerulosclerosis, M = mesangial proliferation, S = segmental sclerosis, SBP = systolic blood pressure, T = tubular atrophy/interstitial fibrosis.

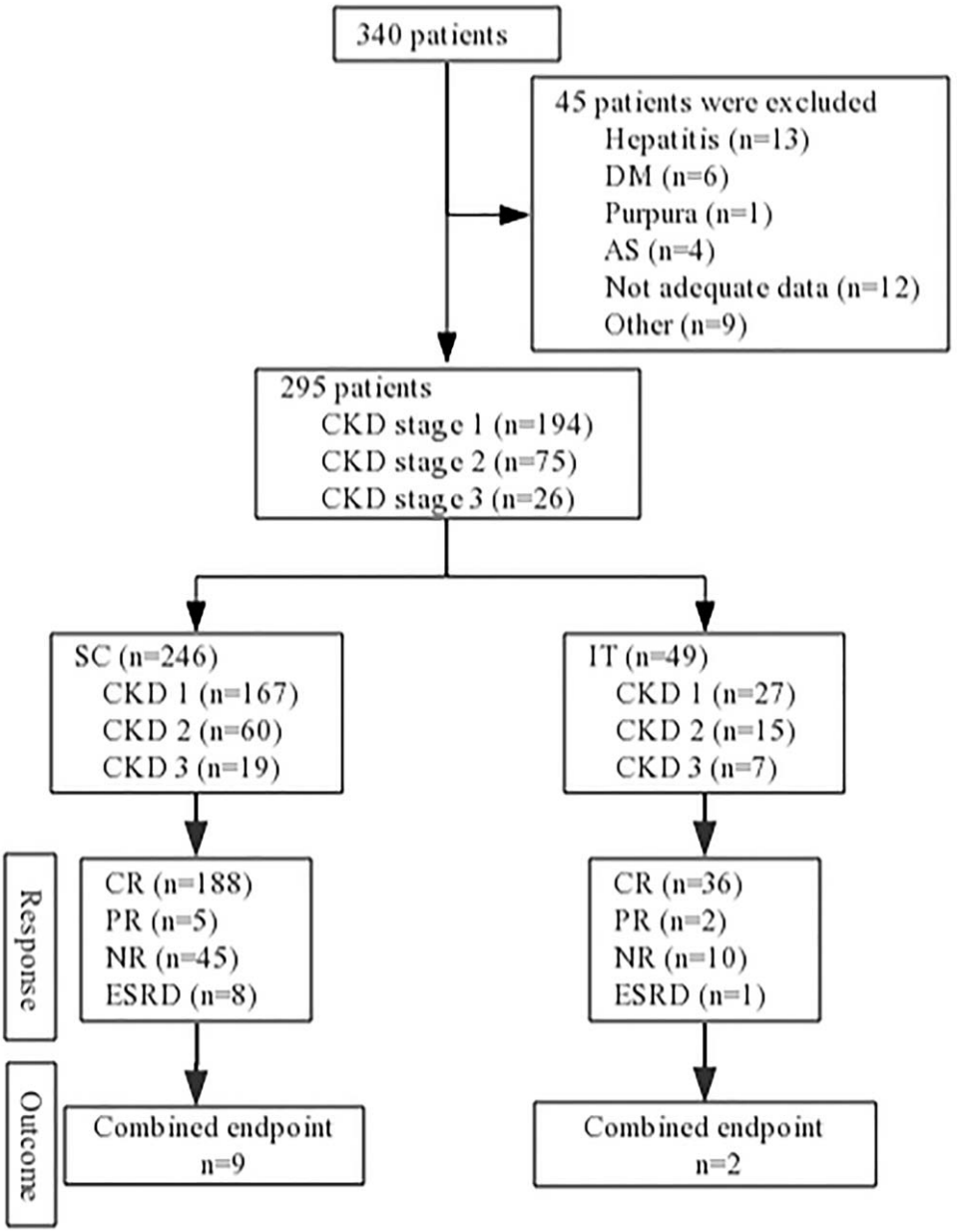

Figure 1. Flow diagram. AS = ankylosing spondylitis, DM = diabetes mellitus, CKD = chronic kidney disease, SC = supportive care group, IT = corticosteroids/immunosuppressive therapy group, CR = complete remission, PR = partial remission, NR = no response, ESRD = end stage renal disease.

patients (3.1%) reached ESRD. Eleven patients (3.7%) reached the combined study endpoint (Table 3). However, no significant differences were observed between the SC and IT groups with respect to CR (76.4% vs 73.5%, $P=.659$), PR (2.0% vs 4.1%, $P=.329$), NR (18.3% vs 20.4%, $P=.728$), and ESRD (3.3% vs 2.0%, $P=1.000$). Additional analyses of stage 1 CKD patients yielded similar results, with 149 of 246 SC group patients (89.2%) and 21 of 49 IT group patients (77.8%) achieving CR by the final visit ($P=.113$). Moreover, there were no stage 1 CKD patients (at baseline) that ended in ESRD during the follow-up period. There was also no significant difference between the SC and IT group CR ratios in stage 2 CKD patients (58.3% vs 66.7%, $P=.556$). A higher CR rate was observed in stage 3 CKD patients in the IT group (71.4%) compared to the SC group (21.1%) ($P=.028$), but the small number of patients may have limited the significance of this result. No statistical difference in ESRD rate was observed in stage 1–3 CKD patients. Moreover, there was no statistically significant difference in the number of patients that reached the combined endpoint in each group (9 patients in the SC group (3.7%) and 2 patients in the IT group (4.1%), $P=1.000$).

3.3. Renal survival

No significant difference was observed between patients in the SC and IT groups with respect to composite endpoint probability calculated from Kaplan–Meier analysis (93.7% vs 94.1%, $P=.808$). Similarly, renal survival rates in the SC group and

Table 3

Response and outcome.

Parameter	All patients n = 295	Therapy groups		*P* value
		SC n = 246	IT n = 49	
Response				
CR	224 (75.9)	188 (76.4)	36 (73.5)	.659
PR	7 (2.4)	5 (2.0)	2 (4.1)	.329
NR	55 (18.6)	45 (18.3)	10 (20.4)	.728
ESRD	9 (3.1)	8 (3.3)	1 (2.0)	1.000
Outcome				
Combined endpoint, no.(%)	11 (3.7)	9 (3.7)	2 (4.1)	1.000
50% decline in eGFR, no. (%)	11 (3.7)	9 (3.7)	2 (4.1)	1.000
ESRD, no. (%)	9 (3.1)	8 (3.3)	1 (2.0)	1.000
CKD 1				
CR	170 (87.6)	149 (89.2)	21 (77.8)	.113
PR	5 (2.6)	3 (1.8)	2 (7.4)	.143
NR	19 (9.8)	15 (9.0)	4 (14.8)	.311
Combined endpoint	1 (0.5)	1 (0.6)	0	1.000
CKD 2				
CR	45 (60.0)	35 (58.3)	10 (66.7)	.556
PR	2 (2.7)	2 (3.3)	0 (0)	1.000
NR	24 (32.0)	20 (33.3)	4 (26.7)	.762
ESRD	4 (5.3)	3 (5.0)	1 (6.7)	1.000
Combined endpoint	5 (6.7)	3 (5.0)	2 (13.3)	.260
CKD 3				
CR	9 (34.6)	4 (21.1)	5 (71.4)	.028
NR	12 (46.2)	10 (52.6)	2 (28.6)	.391
ESRD	5 (19.2)	5 (26.3)	0 (0)	.278
Combined endpoint	5 (19.2)	5 (26.3)	0 (0)	.278

CKD = chronic kidney disease, CR = complete remission, ESRD = end stage renal disease, IT = immunosuppressive therapy, NR = no response, PR = partial remission, SC = supportive care group.

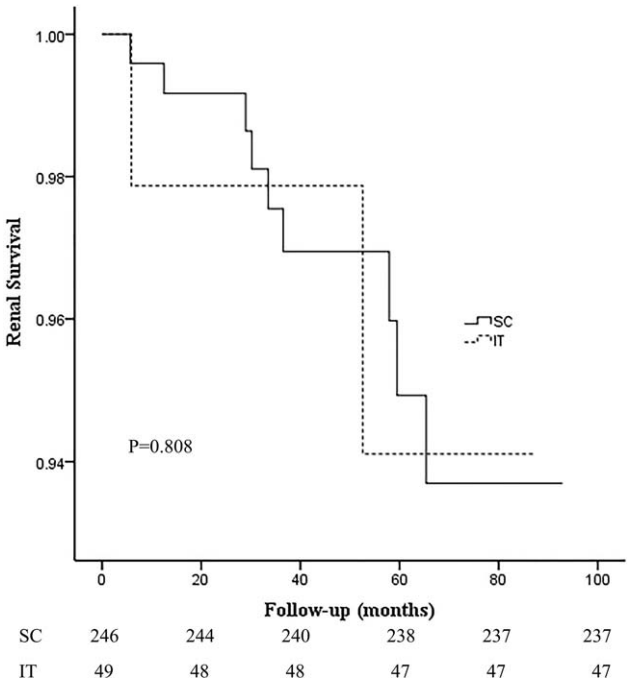

Figure 2. Kaplan–Meier analysis for the composite endpoint probability in SC and IT groups. Note: the composite endpoint was a 50% decline in eGFR and/or ESRD. SC = supportive care group, IT = corticosteroids/immunosuppressive therapy group.

IT group were 97.6% vs 97.9% ($P = .529$) after 3 years and 94.9% versus 94.1% ($P = .392$) after 5 years (Fig. 2). As shown in Figure 3A, renal survival rates were remarkably higher in early stage CKD patients (CKD 1 > CKD 2 > CKD 3, $P < .001$). However, we observed no benefits of immunosuppressant treatment in renal survival in stage 1, 2, or 3 CKD patients with mild proteinuria ($P = .725$, .223, or .160; Fig. 3B and D). Segmental sclerosis and glomerulosclerosis subgroup analysis showed no significant differences between SC and IT group patients in S0 (99.4% vs 95.2%, $P = .105$), S1 (90.9% vs 96.4%, $P = .370$), G0 (99.5% vs 100.0%, $P = .741$), or G1/G2 (70.4% vs 88.2%, $P = .247$).

3.4. Predictive factors of renal outcome

Univariate analysis showed that hypertension, serum creatinine, eGFR, CKD stage at baseline, and the presence of segmental sclerosis (S1), tubular atrophy/interstitial fibrosis (T1/2), and glomerulosclerosis (G1/2) were significantly associated with increased renal outcome risk in this study. However, the multivariable model included only segmental sclerosis (HR 9.55, 95% CI 1.04–88.16, $P = .047$) and glomerulosclerosis (HR 21.09, 95% CI 1.39–320.53, $P = .028$) as independent predictive factors of renal survival (Table 4).

4. Discussion

IgAN is the most common cause of ESRD in adult patients with primary glomerulonephritis worldwide. It is generally thought

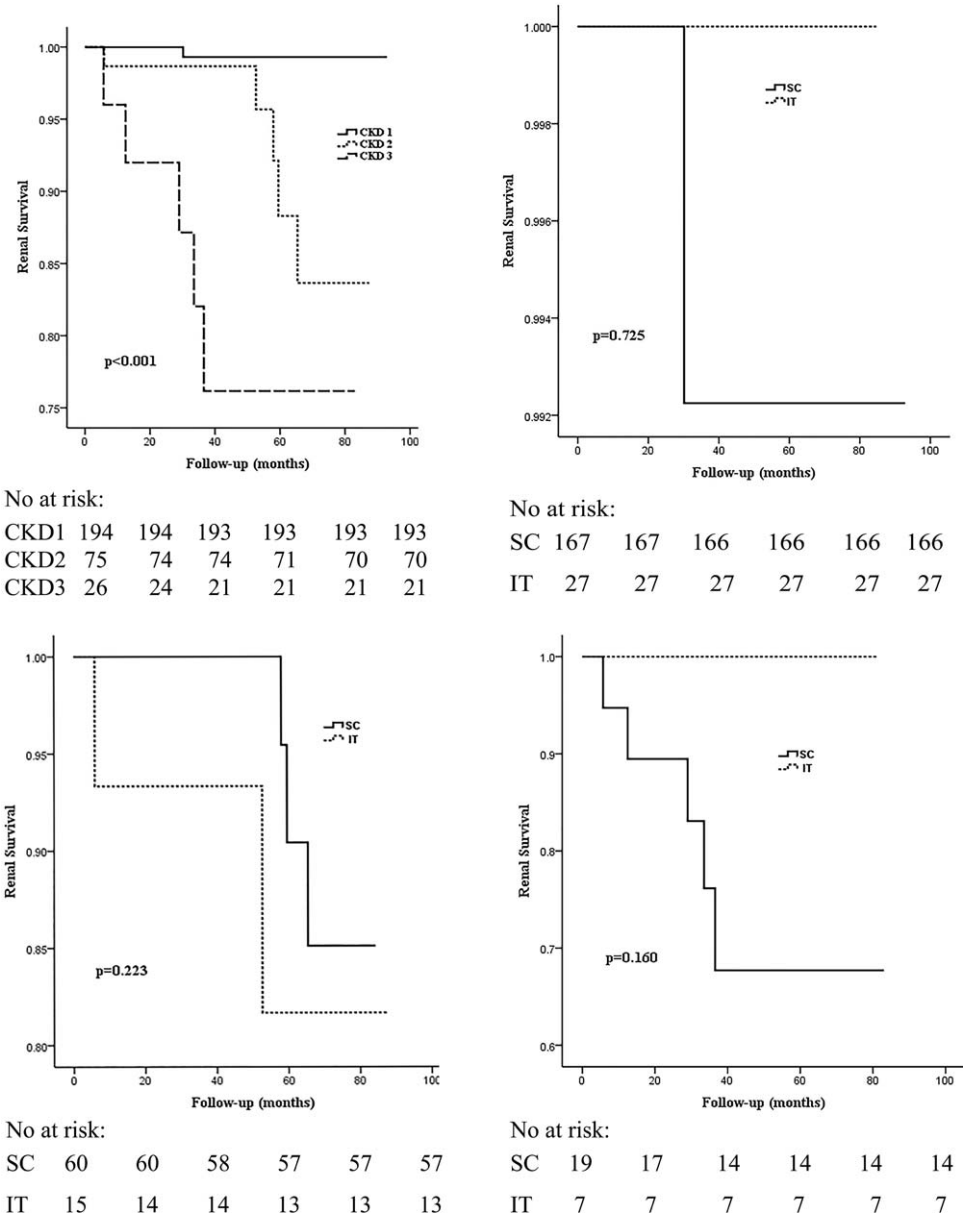

Figure 3. Kaplan–Meier analysis for the composite endpoint probability in different CKD stages. Note: the composite endpoint was a 50% decline in eGFR and/or ESRD. (A) Kidney survival rates in CKD stage 1, 2, and 3 groups. (B) Kidney survival rates in SC and IT group patients with stage 1 CKD. (C) Kidney survival rates in SC and IT group patients with stage 2 CKD. (D) Kidney survival rates in SC and IT group patients with stage 3 CKD. SC = supportive care group; IT = corticosteroids/immunosuppressive therapy group.

that corticosteroid therapy may decrease the risk of progression in high-risk IgAN patients with eGFR >50 mL/min per 1.73 m^2 and proteinuria >1 g/d despite 6 months of supportive therapy.[4] However, the use of corticosteroids and immunosuppressive therapy in patients with mild proteinuria (<1 g/d) has not been studied. Nam et al reported that the risk of developing adverse renal events was remarkably lower in patients with time-averaged proteinuria (TA-P) < 1 g/d compared to those with TA-P >1 g/d.[8] Previous studies evaluating immunosuppressive therapy did not observe IgAN patients with proteinuria < 1 g/d separately, although they included patients with proteinuria between 0.75 and 1 g/d.[6,9] Due to heterogeneous disease manifestation, various treatment strategies could be applied for patients with proteinuria < 1 g/d. Therefore, we performed this study to analyze the effect of corticosteroids and immunosuppressive therapy in IgAN patients with mild proteinuria in order to inform choosing the optimal treatment strategy for IgAN patients.

Currently, there are no recommendations for the best IgAN treatment strategy due to controversial reports about corticosteroid and immunosuppressive therapy.[10] The KDIGO guideline suggests corticosteroid use for patients with persistent proteinuria despite optimized RASi treatment. However, the evidence supporting this guideline is limited (2C).[4] Moreover, corticosteroid or immunosuppressive therapy is also applied to a portion of IgAN patients with proteinuria < 1 g/d because of active clinical or pathological manifestations such as cellular or

Table 4

Cox Proportional Hazard Model for the primary endpoint in IgA nephropathy patients.

	Univariable		Multivariable	
Risk Factor	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Gender				
Female	1 (referent)			
Male	0.65 (0.17–2.44)	.522		
Age	1.06 (1.00–1.12)	.056	1.04 (0.94–1.16)	.420
Hypertension	5.99 (1.75–20.52)	.004	1.98 (0.38–10.25)	.414
Urinary protein	0.21 (0.02–2.47)	.213	0.04 (0.00–1.25)	.067
Serum creatinine	1.03 (1.02–1.05)	<.001	0.99 (0.93–1.06)	.830
eGFR	0.95 (0.92–0.97)	<.001	1.04 (0.91–1.20)	.579
M1	31.86 (0.06–17931)	.284		
E1	0.05 (0.00–1.8E+20)	.905		
S1	8.76 (1.89–40.68)	.006	9.55 (1.04–88.16)	.047
T1/T2	40.11 (10.36–155)	<.001	4.26 (0.51–35.52)	.179
C1/C2	0.57 (0.07–4.42)	.587	3.04 (0.13–74.00)	.494
G1/G2	72.21 (9.19–567.47)	<.001	21.09 (1.39–320.53)	.028
CKD 1	1 (Referent)			
CKD 2	14.56 (1.70–124.74)	.015	33.67 (0.18–6405.02)	.189
CKD3a	49.53 (5.75–426.55)	<.001	192.29 (0.06–587037)	.199

95% CI = 95% confidence interval, C = crescents, CKD = chronic kidney disease, E = endocapillary proliferation, eGFR = estimated glomerular filtration rate, G = glomerulosclerosis, HR = hazard ratio, M = mesangial proliferation, S = segmental sclerosis, T = tubular atrophy/interstitial fibrosis.

fibrocellular crescents, necrotizing lesions, endocapillary proliferation, or a rapid decline of renal function. However, the risk of serious adverse events, such as severe infections and incapacitating bone and endocrine disorders, is notably higher during immunosuppressant use. Given that only a few published studies have discussed the effect of corticosteroid and immunosuppressive therapy in IgAN patients with mild proteinuria, it is difficult to weigh the benefits to long-term renal survival with the potential hazards.[11] Recently, the STOP-IGAN trial, VALIGA cohort study, and several other studies indicated that corticosteroids/immunosuppressants had no desired benefits over renin angiotensin system blockade (RASB) treatment.[6,12,13,9] However, other studies found that corticosteroids/immunosuppressants could improve renal outcomes, such as increased proteinuria remission, decreased eGFR decline, and delayed progression to ESRD,[14,15,16,17] especially in Asian patients. In the present study, we found no favorable effect of corticosteroids or immunosuppressive therapy over optimal supportive care in IgAN patients with mild proteinuria. Moreover, Kaplan–Meier analysis also suggested that renal survival in SC and IT group patients was comparable (94.1% vs 93.7%, $P = .808$). These findings are concordant with the KDIGO guidelines. Therefore, based on our data, supportive care alone might be enough for IgAN patients with mild proteinuria (< 1 g/d), and the addition of immunosuppressive drugs would not benefit these patients.

Our results suggested that baseline eGFR levels were associated with treatment group. We also observed that no stage 1 CKD patients with mild proteinuria progressed into ESRD during the follow-up period (49.46 ± 24.35 months). Prognosis of stage 1 CKD patients was significantly better than those in stage 2 or 3. It should be noted that only a small number of stage 3 CKD patients were recruited in this study. Nevertheless, the CR rate in stage 3 CKD patients in the IT group (71.4%) was much higher than in the SC group (21.1%) ($P = .028$). Furthermore, no stage 3 CKD patient in the IT group reached ESRD, while 5 patients in the SC group (26.3%) ended in ESRD. This finding is consistent with previous reports[16] that immunosuppressive treatment, compared with supportive treatment, may improve short-term renal outcomes in advanced IgAN patients. However, the small number of stage 3 CKD patients enrolled in this study potentially biased these results.

Prior studies have noted the importance of pathological changes on kidney disease prognosis. Most previous studies focused on the association of segmental sclerosis, tubular atrophy/interstitial fibrosis (T), and renal survival.[7] Recently, several reports have shown that global glomerulosclerosis is an independent risk factor for ESRD of IgAN.[18] In accordance with previous results, we found that segmental sclerosis (HR 9.55, 95% CI 1.04–88.16) and glomerulosclerosis (HR 21.09, 95% CI 1.39–320.53) were significantly associated with renal outcome using Cox multivariate analysis. However, no significant differences were observed between patients in the SC and IT groups in S0 (99.4% vs 95.2%, $P = .105$), S1 (90.9% vs 96.4%, $P = .370$), G0 (99.5% vs 100.0%, $P = .741$), or G1/G2 (70.4% vs 88.2%, $P = .247$) according to Kaplan–Meier analysis of segmental sclerosis and glomerulosclerosis subgroups. Therefore, additional studies are required to confirm these findings (Table 4).

This study had a few notable limitations. This was a small size retrospective study and all participants were Chinese. Thus, these results should be interpreted with caution, especially if extrapolating to other patient populations. Errors or missing data are inevitable. A longer follow-up period (more than 10 years) may be needed to achieve more definitive conclusions due to the slow progression of IgAN. Therefore, large-scale, multicenter, long-term follow up clinical studies are needed to achieve a more scientific management of IgAN patients.

5. Conclusion

The results of this study indicate that corticosteroids or immunosuppressants were not superior to optimal supportive care in IgA nephropathy patients with mild proteinuria.

Author contributions

(1) Conception and design: Gaiqin Pei, Yi Tang, Wei Qin; (2) Administrative support: Gaiqin Pei, Jiaxing Tan, Li Tan,

Zhengxia Zhong; (3) Collection and assembly of data: Gaiqin Pei, Jiaxing Tan, Li Tan, Zhengxia Zhong, Ling Zhou, Changyun Chen, Wei Qin; (4) Data analysis and interpretation: Gaiqin Pei, Yi Tang, Li Tan, Zhengxia Zhong, Ling Zhou, Changyun Chen, Wei Qin; (5) Manuscript writing: Gaiqin Pei, Yi Tang, Li Tan, Wei Qin; (6) Final approval of manuscript: all authors.

References

[1] Barbour S, Feehally J. An update on the treatment of IgA nephropathy. Curr Opin Nephrol Hypertens 2017;26:319–26.

[2] Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med 2013;368: 2402–14.

[3] Coppo R. Corticosteroids in IgA nephropathy: lessons from recent studies. J Am Soc Nephrol 2017;28:25–33.

[4] Kidney disease improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Int Suppl 2012;2:209–17.

[5] Gutierrez E, Zamora I, Ballarin JA, et al. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol 2012;23:1753–60.

[6] Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med 2015;373: 2225–36.

[7] Soares MFS, Roberts ISD. Histologic classification of IgA nephropathy: past, present, and future. Semin Nephrol 2018;38:477–84.

[8] Nam KH, Kie JH, Lee MJ, et al. Optimal proteinuria target for renoprotection in patients with IgA nephropathy. PloS One 2014;9: e101935.

[9] Rauen T, Fitzner C, Eitner F, et al. Effects of two immunosuppressive treatment protocols for IgA nephropathy. J Am Soc Nephrol 2018; 29:317–25.

[10] Lafayette RA, Kelepouris E. Immunoglobulin a nephropathy: advances in understanding of pathogenesis and treatment. Am J Nephrol 2018;47 (Suppl. 1):43–52.

[11] Al-Lawati AI, Reich HN. Is there a role for immunosuppression in immunoglobulin a nephropathy? Nephrol Dial Transplant 2017;32 (Suppl. 1):i30–6.

[12] Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA nephropathy: a retrospective analysis from the VALIGA Study. J Am Soc Nephrol 2015;26:2248–58.

[13] Frisch G, Lin J, Rosenstock J, et al. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. Nephrol Dial Transplant 2005;20:2139–45.

[14] Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the testing randomized clinical trial. JAMA 2017;318:432–42.

[15] Pozzi C. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized controlled trial. J Am Soc Nephrol 2004;15:157–63.

[16] Tan L, Tang Y, Peng W, et al. Combined immunosuppressive treatment may improve short-term renal outcomes in Chinese patients with advanced IgA nephropathy. Kidney Blood Press Res 2018;43:1333–43.

[17] Pozzi C, Andrulli S, Pani A, et al. Addition of azathioprine to corticosteroids does not benefit patients with IgA nephropathy. J Am Soc Nephrol 2010;21:1783–90.

[18] Peng W, Tang Y, Tan L, et al. Crescents and global glomerulosclerosis in Chinese IgA nephropathy patients: a five-year follow-up. Kidney Blood Press Res 2019;44:103–12.